ENDURONYL - methyclothiazide and deserpidine tablet
ENDURONYL FORTE - methyclothiazide and deserpidine tablet
Abbott Laboratories

WARNING:
This fixed combination drug is not indicated for initial therapy of hypertension. Hypertension requires therapy titrated to the individual patient. If the fixed combination represents the dosage so determined, its use may be more convenient in patient management. The treatment of hypertension is not static, but must be reevaluated as conditions in each patient warrant.

DESCRIPTION

ENDURONYL tablets are an orally administered combination of Enduron® (methyclothiazide) and deserpidine. ENDURONYL tablets are available in two dosage strengths. ENDURONYL tablets contain methyclothiazide 5 mg and deserpidine 0.25 mg. ENDURONYL FORTE tablets contain methyclothiazide 5 mg and deserpidine 0.5 mg.

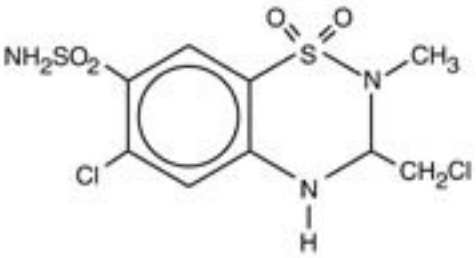
Inactive Ingredients

ENDURONYL Tablets
Corn starch, D&C Yellow No. 10, FD&C Yellow No. 6, lactose, magnesium stearate and talc.

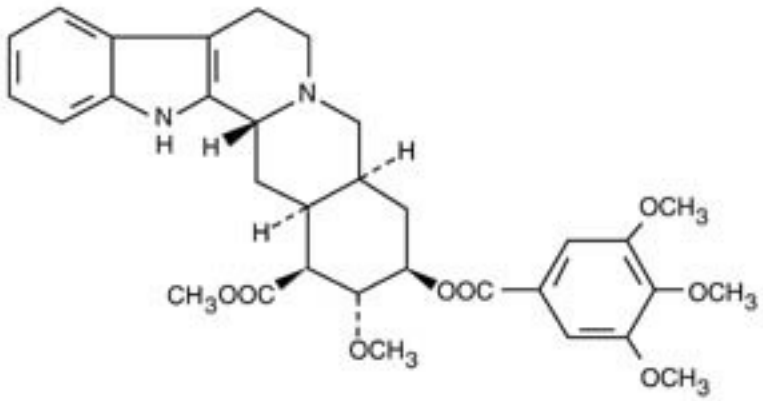
ENDURONYL FORTE Tablets
Corn starch, iron oxide, lactose, magnesium stearate and talc.

Methyclothiazide is an oral diuretic-antihypertensive of the benzothiadiazine (thiazide) class of drugs. It occurs as a white to practically white crystalline powder which is basically odorless and has a molecular weight of 360.25. Methyclothiazide is very slightly soluble in water and chloroform, and slightly soluble in alcohol. Chemically, methyclothiazide is represented as 6-chloro-3-(chloromethyl)-3,4-dihydro-2-methyl-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide.

Deserpidine is a purified rauwolfia alkaloid. It occurs as a white to light yellow crystalline powder and has a molecular weight of 578.64. Deserpidine is insoluble in water and very slightly soluble in alcohol. Chemically, deserpidine is identified as 17α-methoxy-18β-[(3,4,5-trimethoxybenzoyl)oxy]-3β,20α-yohimban-16β-carboxylic acid methyl ester. The structural formulas are:



Methyclothiazide



Deserpidine

CLINICAL PHARMACOLOGY

The combined antihypertensive actions of methyclothiazide and deserpidine result in a total clinical antihypertensive effect which is greater than can ordinarily be achieved by either drug given individually.

Methyclothiazide

The diuretic and saluretic effects of methyclothiazide result from a drug-induced inhibition of the renal tubular reabsorption of electrolytes. The excretion of sodium and chloride is greatly enhanced. Potassium excretion is also enhanced to a variable degree, as it is with the other thiazides. Although urinary excretion of bicarbonate is increased slightly, there is usually no significant change in urinary pH. Methyclothiazide has a per mg natriuretic activity approximately 100 times that of the prototype thiazide, chlorothiazide. At maximal therapeutic dosages, all thiazides are approximately equal in their diuretic/natriuretic effects.

There is significant natriuresis and diuresis within 2 hours after administration of a single dose of methyclothiazide. These effects reach a peak in about 6 hours and persist for 24 hours following oral administration of single dose.
Like other benzothiadiazines, methyclothiazide also has antihypertensive properties, and may be used for this purpose either alone or to enhance the antihypertensive action of other drugs. The mechanism by which the benzothiadiazines, including methyclothiazide, produce a reduction of elevated blood pressure is not known. However, sodium depletion appears to be involved.

Deserpidine
The pharmacologic actions of deserpidine are essentially the same as those of other active rauwolfia alkaloids. Deserpidine probably produces its antihypertensive effects through depletion of tissue stores of catecholamines (epinephrine and norepinephrine) from peripheral sites. By contrast, its sedative and tranquilizing properties are thought to be related to depletion of 5-hydroxytryptamine from the brain. The antihypertensive effect is often accompanied by bradycardia. There is no significant alteration in cardiac output or renal blood flow. The carotid sinus reflex is inhibited, but postural hypotension is rarely seen with the use of conventional doses of deserpidine alone.
Deserpidine, like other rauwolfia alkaloids, is characterized by slow onset of action and sustained effect which may persist following withdrawal of the drug.

Pharmacokinetics and Metabolism

Methyclothiazide
Methyclothiazide is rapidly absorbed and slowly eliminated by the kidneys as intact drug but primarily as an inactive metabolite. Additional information on the pharmacokinetics is not known at this time.

Deserpidine
Information is limited on the human pharmacokinetics of the rauwolfia alkaloids. Rauwolfia alkaloids appear to be widely distributed in body tissues, especially adipose tissue. They also cross the blood-brain barrier. Rauwolfia alkaloids are extensively metabolized. The unchanged alkaloid and the metabolites are excreted slowly in urine and feces.

INDICATIONS AND USAGE
ENDURONYL (methyclothiazide and deserpidine) is indicated in the treatment of mild to moderately severe hypertension (see **BOXED WARNING**). In many cases ENDURONYL tablets alone produces an adequate reduction of blood pressure. In resistant or unusually severe cases ENDURONYL tablets also may be supplemented with more potent antihypertensive agents. When administered with ENDURONYL tablets, more potent agents can be given at reduced dosage to minimize undesirable side effects.

CONTRAINDICATIONS
Methyclothiazide is contraindicated in patients with anuria and in patients with a history of hypersensitivity to this or other sulfonamide-derived drugs.
Deserpidine is contraindicated in patients with known hypersensitivity, history of mental depression especially with suicidal tendencies, active peptic ulcer, and ulcerative colitis. It is also contraindicated in patients receiving electroconvulsive therapy.

WARNINGS

Methyclothiazide
Methyclothiazide shares with other thiazides the propensity to deplete potassium reserves to an unpredictable degree.
There have been isolated reports that certain nonedematous individuals developed severe fluid and electrolyte derangements after only brief exposure to normal doses of thiazide and nonthiazide diuretics.
Thiazides should be used with caution in patients with renal disease or significant impairment of renal function, since azotemia may be precipitated and cumulative drug effects may occur.
Thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.
Sensitivity reactions may occur in patients with a history of allergy or bronchial asthma.
The possibility of exacerbation or activation of systemic lupus erythematosus has been reported.
Hyperuricemia may occur or frank gout may be precipitated in certain patients receiving thiazide therapy.

Deserpidine
Deserpidine differs slightly in chemical structure from reserpine; however, its actions, indications, cautions, and adverse reactions are common to the class of rauwolfia alkaloids. Reserpine may cause mental depression. Recognition of depression may be difficult because this condition may often be disguised by somatic complaints (Masked Depression). The drug should be discontinued at first signs of depression such as despondency, early morning insomnia, loss of appetite, impotence, or self-deprecation. Drug-induced depression may persist for several months after drug withdrawal and may be severe enough to result in suicide.

PRECAUTIONS

General

Methyclothiazide
All patients should be observed for other clinical signs of electrolyte imbalances such as dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting.

Hypokalemia may develop, especially with brisk diuresis, when severe cirrhosis is present, during concomitant use of corticosteroids or ACTH, or after prolonged therapy.

Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Hypokalemia may be avoided or treated with the intake of potassium supplements or foods containing a high potassium content.

Any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease). Dilutional hyponatremia may occur in endematous patients in hot weather. Appropriate therapy is water restriction rather than administration of salt, except in rare instances when the hyponatremia is life threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

Latent diabetes mellitus may become manifest during thiazide administration.

The antihypertensive effects of the drug may be enhanced in the postsympathectomy patient.

If progressive renal impairment becomes evident as indicated by a rising-nonprotein nitrogen or blood urea nitrogen, a careful reappraisal of therapy is necessary with consideration given to withholding or discontinuing diuretic therapy.

Thiazide diuretics have been shown to increase the urinary excretion of magnesium; this may result in hypomagnesemia.

Thiazides may decrease urinary calcium excretion and may cause intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Marked hypercalcemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.

Thiazides may cause increased concentrations of total serum cholesterol, total triglycerides, and low-density lipoproteins in some patients. Use thiazides with caution in patients with moderate or high cholesterol concentrations and in patients with elevated triglyceride levels.

Deserpidine
Because rauwolfia preparations increase gastrointestinal motility and secretion, this drug should be used cautiously in patients with a history of peptic ulcer, ulcerative colitis, or gallstones, where biliary colic may be precipitated.

Caution should be exercised when treating hypertensive patients with renal insufficiency, since they adjust poorly to lowered blood pressure levels.

Preoperative withdrawal of deserpidine does not assure that circulatory instability will not occur. It is important that the anesthesiologist be aware of the patient's drug intake and consider this in the overall management, since hypotension has occurred in patients receiving rauwolfia preparations. Anticholinergic and/or adrenergic drugs (metaraminol, norepinephrine) have been employed to treat adverse vagocirculatory effects.

Information for Patients

Patients should inform their doctor if they have: 1) had an allergic reaction to methyclothiazide, other diuretics, or deserpidine; 2) asthma; 3) kidney disease; 4) liver disease; 5) gout; 6) systemic lupus erythematosus; or 7) been taking other drugs such as cortisone, digitalis, lithium carbonate, or drugs for diabetes.
The physician should inform patients of possible side effects and caution the patient to report any of the following symptoms of electrolyte imbalance: dryness of mouth, thirst, weakness, tiredness, drowsiness, restlessness, muscle pains or cramps, nausea, vomiting, or increased heart rate.
The patient and his family should be warned of the possibility of depression. If signs of despondency, early morning insomnia, loss of appetite, impotence, or self-deprecation appear, the drug should be discontinued and the physician consulted.
Patients who engage in potentially hazardous activities such as operating machinery or driving motor vehicles should be warned about possible central nervous system (CNS) side effects.
The physician should advise the patient to take this medication every day as directed. Physicians should also caution patients that drinking alcohol can increase the chance of dizziness and other CNS-depressant effects.

Laboratory Tests
Initial and periodic determination of serum electrolytes should be performed at appropriate intervals for the purpose of detecting possible electrolyte imbalances such as hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when a patient is vomiting excessively or receiving parenteral fluids.

Drug Interactions

Methyclothiazide
Hypokalemia can sensitize or exaggerate the response of the heart to the toxic effects of *digitalis* (e.g., increased ventricular irritability).

Hypokalemia may develop during concomitant use of *steroids* or *ACTH*.

Insulin requirements in diabetic patients may be increased, decreased, or unchanged.

Thiazides may decrease arterial responsiveness to *norepinephrine*. This diminution is not sufficient to preclude effectiveness of the pressor agent for therapeutic use.

Non-steroidal Anti-inflammatory Drugs– In some patients the administration of a non-steroidal anti-inflammatory agent can reduce the diuretic, natriuretic, and antihypertensive effects of loop, potassium-sparing, and thiazide diuretics. Therefore, when Enduronyl tablets and non-steroidal anti-inflammatory agents are used concomitantly, the patient should be observed closely to determine if the desired effect of the diuretic is obtained.

Thiazide drugs may increase the responsiveness to *tubocurarine*.

Lithium renal clearance is reduced by thiazides, increasing the risk of lithium toxicity.

Thiazides may add to or potentiate the action of *other antihypertensive drugs*. Potentiation occurs with ganglionic or peripheral adrenergic blocking drugs.

Deserpidine
Use deserpidine cautiously with *digitalis* and *quinidine* since cardiac arrhythmias have occurred with rauwolfia preparations.

Hypotensive effects of rauwolfia alkaloids may be enhanced when used concurrently with other *antihypertensive agents*, *diuretics*, or *phenothiazine derivatives*, therefore, careful titration of dosage is necessary.

Additive CNS-depressant effects can occur when rauwolfia alkaloids are taken concomitantly with other *CNS-depressant agents* or *alcohol*.

Monoamine oxidase inhibitors should be avoided or used with extreme caution.

Drug/Laboratory Test Interactions
Thiazides may decrease serum PBI levels without signs of thyroid disturbance.
Thiazides should be discontinued before carrying out tests for parathyroid function.
Rauwolfia alkaloids have been reported to interfere with assay procedures for the determination of urinary 17-hydroxycorticosteroids and 17-ketosteroids.

Carcinogenesis, Mutagenesis, Impairment of Fertility
No long-term data are available for methyclothiazide or deserpidine concerning the potential for carcinogenicity. No adequate studies have been done to determine the mutagenic potential of methyclothiazide or deserpidine, or their effects on fertility.

Animal Tumorigenicity
Although there are no studies demonstrating that deserpidine is an animal tumorigen, it is a prolactin stimulator and structurally related to reserpine. Rodent studies have shown that reserpine is an animal tumorigen, causing an increased incidence of mammary fibroadenomas in female mice, malignant tumors of the seminal vesicles in male mice, and malignant adrenal medullary tumors in male rats. These findings arose in 2 year studies in which the drug was administered in the feed at concentrations of 5 and 10 ppm - about 100 to 300 times the usual human dose. The breast neoplasms are thought to be related to reserpine's prolactin-elevating effect. Several other prolactin-elevating drugs have also been associated with an increased incidence of mammary neoplasia in rodents.

The extent to which these findings indicate a risk to humans is uncertain. Tissue culture experiments show that about one-third of human breast tumors are prolactin-dependent *in vitro*, a factor of considerable importance if the use of the drug is contemplated in a patient with previously detected breast cancer. The possibility of an increased risk of breast cancer in reserpine users has been studied

extensively; however, no firm conclusion has emerged. Although a few epidemiologic studies have suggested a slightly increased risk (less than two fold in all studies except one) in women who have used reserpine, other studies of generally similar design have not confirmed this. Epidemiologic studies conducted using other drugs (neuroleptic agents) that, like reserpine, increase prolactin levels and, therefore, would be considered rodent mammary carcinogens, have not shown an association between chronic administration of the drug and human mammary tumorigenesis. While long-term clinical observation has not suggested such an association, the available evidence is considered too limited to be conclusive at this time. An association of reserpine intake with pheochromocytoma or tumors of the seminal vesicles has not been explored.

Pregnancy Category C
Animal reproduction studies have not been conducted with methyclothiazide or deserpidine. It is also not known whether methyclothiazide or deserpidine can cause fetal harm when administered to a pregnant woman. Methyclothiazide and deserpidine should be given to a pregnant woman only if clearly needed.

Nonteratogenic Effects

Methyclothiazide
Thiazides cross the placental barrier and appear in cord blood. The use of thiazides in pregnant women requires that the anticipated benefit be weighed against possible hazards to the fetus. These hazards include fetal or neonatal jaundice, thrombocytopenia, and possible other adverse reactions that have occurred in the adult.

Deserpidine
Rauwolfia alkaloids are known to cross the placental barrier, to enter the fetal circulation, and to appear in cord blood. Increased respiratory secretions, nasal congestion, cyanosis and anorexia may occur in neonates of rauwolfia alkaloid-treated mothers.

Nursing Mothers
Methyclothiazide and deserpidine are excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from ENDURONYL tablets, a decision should be made whether to discontinue nursing or to discontinue the drug taking into account the importance of the drug to the mother.

Pediatric Use
Safety and effectiveness in children have not been established.

ADVERSE REACTIONS
Adverse reactions are usually reversible upon reduction of dosage or discontinuation of ENDURONYL tablets. Whenever adverse reactions are moderate or severe, it may be necessary to discontinue the drug.
The following adverse reactions have been observed, but there has not been enough systematic collection of data to support an estimate of their frequency. Consequently, the reactions are categorized by organ system and are listed in decreasing order of severity and not frequency.

Methyclothiazide

Body as a Whole
Headache, cramping, weakness.

Cardiovascular System
Orthostatic hypotension (may be potentiated by alcohol, barbiturates, or narcotics).

Digestive System
Pancreatitis, jaundice (intrahepatic cholestatic), sialadenitis, vomiting, diarrhea, nausea, gastric irritation, constipation, anorexia.

Hemic and Lymphatic System
Aplastic anemia, hemolytic anemia, agranulocytosis, leukopenia, thrombocytopenia.

Hypersensitivity Reactions
Anaphylactic reactions, necrotizing angiitis (vasculitis, cutaneous vasculitis), Stevens-Johnson syndrome, respiratory distress (including pneumonitis and pulmonary edema), fever, purpura, urticaria, rash, photosensitivity.

Metabolic and Nutritional Disorders
Hyperglycemia, hyperuricemia, electrolyte imbalance (see **PRECAUTIONS**), hypercalcemia.

Nervous System
Vertigo, dizziness, paresthesias, muscle spasm, restlessness.

Special Senses
Transient blurred vision, xanthopsia.

Urogenital System
Glycosuria.

Deserpidine

Body as a Whole
Headache.

Cardiovascular System
Arrhythmias (particularly when used concurrently with digitalis or quinidine), syncope, angina-like symptoms, bradycardia, fluid retention.

Digestive System
Vomiting, diarrhea, nausea, anorexia, dryness of mouth, hypersecretion, increased motility, increased salivation.

Hemic and Lymphatic System
Thrombocytopenic purpura.

Metabolic and Nutritional Disorders
Weight gain.

Musculoskeletal System
Muscular aches.

Nervous System
Rare parkinsonian syndrome and other extrapyramidal tract symptoms, dizziness, paradoxical anxiety, depression, nervousness, nightmares, dull sensorium, drowsiness, decreased libido.

Respiratory System
Asthma in asthmatic patients, dyspnea, epistaxis, nasal congestion.

Skin and Appendages
Rash, pruritus, flushing of skin.

Special Senses
Deafness, optic atrophy, glaucoma, uveitis, conjunctival injection.

Urogenital System
Nonpuerperal lactation, impotence, dysuria, gynecomastia, breast engorgement.

OVERDOSAGE

Symptoms of thiazide overdosage include electrolyte imbalance and signs of potassium deficiency such as confusion, dizziness, muscular weakness, and gastrointestinal disturbances. General supportive measures including replacement of fluids and electrolytes may be indicated in treatment of overdosage.
An overdosage of deserpidine is characterized by flushing of the skin, conjunctival injection, and pupillary constriction. Sedation ranging from drowsiness to coma may occur. Hypotension, hypothermia, central respiratory depression, and bradycardia may develop in cases of severe overdosage. Treatment consists of the careful evacuation of stomach contents followed by the usual procedures for the symptomatic management of CNS depressant overdosage. If severe hypotension occurs, it should be treated with a direct-acting vasopressor (e.g., norepinephrine). If bradycardia becomes marked, especially with cardiac arrhythmia, consider use of atropine or other anticholinergic drug. Because of prolonged effects of deserpidine, the patient should be closely observed for at least 72 hours.

DOSAGE AND ADMINISTRATION

Dosage should be determined by individual titration of ingredients (see **BOXED WARNING**).
Dosage of both components should be carefully adjusted to the needs of the individual patient. Since at least 10 days to 2 weeks may elapse before the full effects of the drugs become manifest, the dosage of the drugs should not be adjusted more frequently.

Two tablet strengths, ENDURONYL (methyclothiazide 5 mg, deserpidine 0.25 mg) and ENDURONYL FORTE (methyclothiazide 5 mg, deserpidine 0.5 mg), each grooved, are provided to permit considerable latitude in meeting the dosage requirements of individual patients.
The following table will help in determining which dose of ENDURONYL or ENDURONYL FORTE tablets best represents the equivalent of the titrated dose.

Daily Dosage of ENDURONYL	Methyclothiazide	Deserpidine
½ tablet	2.5 mg	0.125 mg
1 tablet	5.0 mg	0.250 mg
1½ tablets	7.5 mg	0.375 mg
2 tablets	10.0 mg	0.500 mg

Daily Dosage of ENDURONYL FORTE	Methyclothiazide	Deserpidine
½ tablet	2.5 mg	0.250 mg
1 tablet	5.0 mg	0.500 mg
1½ tablets	7.5 mg	0.750 mg
2 tablets	10.0 mg	1.000 mg

The appropriate dose of ENDURONYL tablets is administered orally, once daily. The usual adult dosage is one lower-strength ENDURONYL tablet daily. Debilitated and elderly patients may require lower doses.
There is no contraindication to combining ENDURONYL tablets with other antihypertensive agents. When other antihypertensive agents are to be added to the regimen, this should be accomplished gradually. Ganglionic blocking agents should be given at only half the usual dose since their effect is potentiated by pretreatment with ENDURONYL tablets.

HOW SUPPLIED
ENDURONYL (methyclothiazide and deserpidine) is supplied as monogrammed, grooved, square-shaped tablets in the following dosage sizes and quantities:
ENDURONYL (5 mg of methyclothiazide and 0.25 mg of deserpidine) yellow tablets bearing the **Abbott"A" logo** and Abbo-Code LS for product identification in bottles of 100 (**NDC** 0074-6838-01).
ENDURONYL FORTE (5 mg of methyclothiazide and 0.5 mg of deserpidine) gray-colored tablets bearing the **Abbott "A" logo** and Abbo-Code LT for product identification in bottles of 100 (**NDC** 0074-6854-01).

Recommended Storage
Store below 86°F (30°C).

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